Milrinone: Is Bolus Bad?

Fontan[1] procedure, first described in 1971 for the management of patients with congenital heart disease with a single anatomical or functional ventricle, has undergone numerous[2] modifications. Total cavopulmonary connection has emerged as the procedure of choice among all. The procedure effectively places the systemic and pulmonary circulation in series by connecting the systemic venous return to the pulmonary arteries without the interposition of an adequate ventricle. The pressure head for both systemic and pulmonary circulations is generated by the single functional systemic ventricle. Postcapillary energy and the negative intrathoracic pressure are the driving forces for the pulmonary circulation. Cardiac output hence is no longer determined by the heart alone but rather by transpulmonary flow, which itself is mainly determined by the pulmonary vascular resistance. Maintenance of adequate cardiac contractility and low pulmonary vascular resistance are vital to maintain the cardiac output.

Milrinone is an intravenously active selective phosphodiesterase III inhibitor which has positive inotropic, vasodilator, and lusitropic[3] properties. It enhances cardiac contractility and reduces systemic as well as pulmonary vascular resistances. This inodilator (inotropy + vasodilatation) property makes milrinone uniquely suitable to maintain and enhance cardiac output in children who undergo Fontan procedure. Milrinone is typically administered initially as a bolus dose ranging from 12.5 μg/kg to 125 μg/kg slowly over 10 min. This is followed by an infusion at the rate of 0.375 μg/kg/min to 0.75 μg/kg/min. There are conflicting reports in the literature regarding the hemodynamic effects of bolus dose.[4,5] The volume of distribution, clearance, and the beta half-lives in children more than one year of age are 0.7 ± 0.2 L/kg, 5.9 ± 2.0 ml/kg/min, and 1.86 ± 2 h, respectively.[6] The initial bolus is given so as to achieve therapeutic plasma concentrations of 100 ng/ml–300 ng/ml and the infusion is continued as to maintain the plasma concentration in the therapeutic range. Milrinone is known not to bind to the cardiopulmonary bypass (CPB) circuitry in contrast to amrinone so it can be administered before weaning of CPB without much loss of the drug. The authors in the current study[7] have compared and analyzed two different dose regimens of milrinone in 116 children undergoing Fontan procedure. In one group (E), milrinone was started as an infusion at the rate of 0.5 μg/kg/min at the beginning of CPB and in another group (L) a bolus of 50 μg/kg was administered 10 min before the separation of CPB followed by an infusion at the rate of 0.5–0.75 μg/kg/min in both groups postoperatively. They have found favorable hemodynamics, less requirement of vasopressors, as well as early discharge from the ICU and the hospital in group E. Interesting observation, is that the overall dose before weaning off the CPB was more in E group than in the L group. The major limitation of this study is not measuring the plasma levels of milrinone, which would have given greater insight into pharmacokinetics of bolus versus infusion regimen both during CPB and post-CPB. The authors claim that the reasons for better hemodynamics in group E may be due to (a) larger overall dose of milrinone, (b) better perfusion during CPB, and (c) anti-inflammatory properties of milrinone. One more challenge in this study is estimation of cardiac output and cardiac index. Estimation of cardiac output by 2D echocardiography is not without the risk of unwanted errors due to (a) altered anatomy and geometry of the ventricle and (b) the increased contribution of negative intrathoracic pressure during spontaneous breathing to the preload and cardiac output. The effect of these errors would probably be dampened when trends are assessed rather than focusing on individual values.

Similar studies in children undergoing various congenital heart surgeries[8] and in adults with pulmonary hypertension undergoing coronary artery bypass graft[9] and and/or valve surgeries on CPB were published with very similar results. However, this study is different from those studies that it is done in Fontan circulation and has shown the benefits of initiating the infusion at the beginning of the CPB. With reduction in the central venous pressure, left atrial pressure and the transpulmonary gradient in comparison to the late group, early regimen has shown beneficial vasodilatory effects in the pulmonary circulation. Further studies with serum levels of milrinone would further elucidate the reason for the differences between the groups.

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Access this article online	
Quick Response Code:	Website: www.annals.in
	DOI: 10.4103/aca.ACA_221_17

How to cite this article: Kulkarni V. Milrinone: is bolus bad?. Ann Card Anaesth 2018;21:141-2.